The Relationship Between Gabapentin and Pregabalin and Posttraumatic Stress Disorder in Burned Servicemembers

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Posttraumatic stress disorder (PTSD) affects approximately 30% of burned Servicemembers returning from Operation Iraqi Freedom/Operation Enduring Freedom. Gabapentin and pregabalin are anticonvulsant drugs that limited evidence suggests may also be effective treatments for some psychological disorders. This study examines the relationship between these anticonvulsants and PTSD development in burned Servicemembers. Drugs received, injury severity score, TBSA burned, length of hospital stay, number of intensive care unit days, number of surgeries, and PTSD Checklist-Military scores and administration dates were collected. Subjects were grouped based on receipt of gabapentin or pregabalin, and the groups were compared. The primary outcome was incidence of a positive screen for PTSD. Because injury severity was significantly different between the two groups, propensity score matching based on injury severity score and TBSA was performed. Two hundred ninety burned Servicemembers received the PTSD Checklist-Military at least 30 days after injury. Of these subjects, 104 received gabapentin, pregabalin, or both and 186 did not. Despite significantly greater injuries, the group that received gabapentin or pregabalin did not develop PTSD at a different rate than those patients who did ($P = .727$). Propensity score matching resulted in 57 patients in each group; there was no difference between these groups in the incidence of PTSD ($P = .663$). These data suggest that gabapentin or pregabalin administration may not affect PTSD development in burned Servicemembers. Many factors influence the development and progression of PTSD, but few drugs have been identified that are effective at treating or preventing PTSD. (J Burn Care Res 2012;33:612–618)

Posttraumatic stress disorder (PTSD) is a psychological disorder that affects approximately 30% of burned US Servicemembers returning from recent combat operations in Overseas Contingency Operations, including Operation Iraqi Freedom in Iraq and Operation Enduring Freedom in Afghanistan.[1] Risk factors that can increase the likelihood of PTSD development include experiencing a traumatic incident in which you fear for your life, injury or fear of injury, and untreated pain.[2–5] PTSD is diagnosed based on the presence and severity of a variety of symptoms, including flashbacks, nightmares, insomnia, emotional disturbance, social withdrawal, forgetfulness, and hyperarousal. These symptoms are defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).[6] PTSD is often accompanied by multiple comorbidities such as chronic pain, substance abuse, depression, and/or anger problems.[7–12]

Treatment of PTSD includes cognitive behavioral therapy and pharmacologic approaches.[13] The nature of the disease, however, and the likely presence of multiple comorbidities, makes effective management of PTSD symptoms challenging. Many classes of drugs have been investigated for efficacy in prophylaxis or treatment of PTSD, including selective serotonin reuptake inhibitors, tricyclic antidepressants, benzodiazepines and other anxiolytic drugs,

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serotonin-potentiating drugs, monoamine oxidase inhibitors, and anticonvulsants.[13–20] Gabapentin and pregabalin are anticonvulsants that limited data suggest may alleviate symptoms of PTSD.

Gabapentin was developed as an alkylated analog of the inhibitory neurotransmitter gamma-aminobutyric acid[21]; however, the primary pharmacologic mechanism of gabapentin is not through gamma-aminobutyric acid receptors.[22] Rather, the antiepileptic effects of gabapentin are mediated through its inhibition of voltage-gated sodium channels, specifically the α2δ-1 subunit.[23–26] Pregabalin was designed as a more potent anticonvulsant that shares the same mechanisms of action as gabapentin.[27] Gabapentin and pregabalin are effective choices for treating seizures and, like other antiepileptic drugs, have been investigated for efficacy in other neurologic conditions. Multiple small trials, many of them open-label trials, have identified antiepileptic drugs such as valproic acid, carbamazepine, lamotrigine, oxcarbazepine, topiramate, pregabalin, and gabapentin as potential treatments for trigeminal neuralgia, postherpetic neuralgia, diabetic neuropathy, migraine, bipolar disorder, neuropathic pain, and anxiety.[19,28] Gabapentin and pregabalin are both approved for treatment of epilepsy and postherpetic neuralgia, and pregabalin is also approved for the treatment of diabetic neuropathy and fibromyalgia; other indications are currently being investigated.[29–33] Gabapentin and pregabalin are often prescribed as adjuvant pain medication, and one study found that gabapentin decreased opioid consumption and pain scores in hospitalized burn patients.[29]

Despite inclusion in numerous review articles about alternative pharmacologic treatments for PTSD and other psychological disorders, there is a dearth of definitive, well-supported evidence for the use of gabapentin, pregabalin, and other anticonvulsants for such indications. Several case studies and smaller studies have suggested that gabapentin reduces PTSD symptoms, with its most significant effects on frequency of nightmares and other sleep disturbances.[34–36] Indeed, gabapentin has been recommended as a third-line medication for the treatment of PTSD-associated nightmares in adults by the Standards of Practice Committee of the American Academy of Sleep Medicine.[37] Pregabalin also decreases pain and improves sleep and mood in patients with postherpetic neuralgia.[38]

The effects of gabapentin and pregabalin on the development of PTSD in combat-wounded Servicemembers have not been investigated. This retrospective study analyzes the relationship between the administration of the anticonvulsants gabapentin and pregabalin and PTSD development in burned Servicemembers.

METHODS

This retrospective study was conducted after institutional review board approval and in accordance with the approved protocol. The population analyzed comprised United State Servicemembers who suffered burns and were treated at the military burn center between 2004 and 2010. Burned Servicemembers who received the PTSD Checklist-Military (PCL-M) at least 30 days postinjury were included in this study.

Data on pregabalin, gabapentin, and opioids received, injury severity score (ISS), TBSA burned, length of hospital stay (LOS), number of intensive care unit (ICU) days, and number of surgeries were collected from patient charts. Morphine equivalent units (MEUs, mg/d) were calculated by adding opioid dosages received in both the operating room and the ward and then dividing by the number of days the patient was in the hospital. All opioid dosages were converted into intravenous morphine equivalents.[39] We also identified the most recent PCL-M score of each subject. The PCL-M is the screening tool for PTSD authorized for use by the U.S. military. It is composed of 17 questions, which the subject must rate 1 (not at all) to 5 (extremely), designed to identify the presence, frequency, and severity of PTSD symptoms, including feelings of reexperiencing, avoidance, dysphoria, and hyperarousal.[11] Possible scores on the PCL-M range from 17 to 85. For this study, a positive screen for PTSD was defined as a score of 44 or above on the PCL-M.[40] Although numerous studies discuss the validity of lower[30–34] or higher[41] cutpoints,[42,43] the score of 44 is the cutoff point considered a positive screen for PTSD at our institution; it is at this score that patients are always referred for additional care. The cut point of 44 has also been recently used in other studies of the combat burn population.[1,4,44,45] All Servicemembers admitted to the burn center are screened for PTSD using the PCL-M upon discharge; however, only those Servicemembers who received the PCL-M screening at least 30 days after injury were included in our analyses.

Subjects were stratified into two groups. One group received the gabapentin and/or pregabalin before their PCL-M was administered, and the other group did not receive gabapentin or pregabalin before their PCL-M was administered. The two groups were then compared to determine whether

there was a difference in the incidence of a positive screen on the PCL-M or the frequency/severity of PTSD symptoms, as indicated by the PCL-M score. Frequency and dosages of gabapentin/pregabalin administration were not analyzed.

Statistical analyses were accomplished using the SAS statistical software package to perform the Wilcoxon's signed-rank test and the χ^2 test to examine differences between the two groups. The Spearman correlation test was used to determine the relationships between gabapentin or pregabalin administration and age, TBSA, ISS, ICU days, LOS, surgeries, MEU (mg/d), and average patient pain score. Statistical significance was defined as $P < .05$. Propensity score matching was then conducted based on ISS and TBSA. Matching resulted in a sample size of 57 in each group. The matched sample data were again analyzed using the Wilcoxon's signed-rank test and the χ test.

RESULTS

Between 2004 and 2010, the United States Army Institute of Surgical Research Burn Center received 785 burned Servicemembers. Of these, 290 received the PCL-M at least 30 days postinjury. One hundred four of these burned Servicemembers received gabapentin or pregabalin, and 186 did not (Figure 1). Subjects receiving gabapentin or pregabalin were more severely injured; they had significantly higher TBSA burned and ISS scores, underwent a significantly higher number of surgeries, spent significantly more days in the ICU, and had significantly longer LOS (Table 1). Patients who received gabapentin or pregabalin also received significantly more morphine equivalents per day throughout their treatment. There was no significant difference between the two groups in patient age or average pain score (Table 1). There was also no significant difference in the prevalence of a positive screen for PTSD between the two groups, $P = .727$. Twenty-six of the 104 (25%) patients who received gabapentin or pregabalin scored ≥44 on the PCL-M compared with 50 of 186 (26.9%) patients who did not receive gabapentin or pregabalin (Table 2). There was no significant difference in the average PCL-M scores of patients who received gabapentin or pregabalin and those who did not, $P = .512$ (Table 2). We did find significant positive correlations between receipt of gabapentin and pregabalin and measures of injury severity, including TBSA, ISS, ICU days, LOS, number of surgeries, and MEU/day ($P < .001$); however, there was no significant correlation between gabapentin and pregabalin administration and the age or average pain scores of the patients (Table 3).

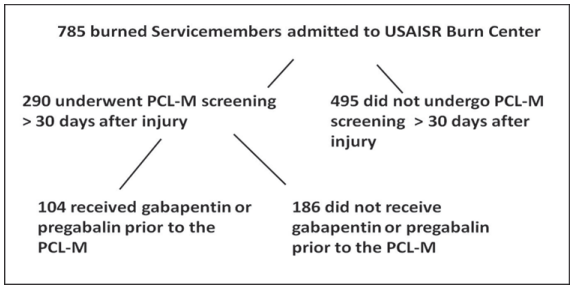

Figure 1. Patient population. Between 2004 and 2010, the United States Army Institute of Surgical Research Burn Center received 785 burned Servicemembers. Of these, 290 received the PTSD Checklist-Military (PCL-M) at least 30 days postinjury. One hundred four of these burned Servicemembers received gabapentin or pregabalin, and 186 did not.

Table 1. Patient demographics, injury severity parameters, and drugs received

	Gabapentin or Pregabalin (n = 104)	No Gabapentin or Pregabalin (n = 186)	*P*
Age	25.6 ± 6.0	25.5 ± 6.2	.223
TBSA	32.1 ± 21.3*	14.2 ± 14.4*	<.0001
ISS	23.8 ± 13.6*	11.56 ± 10.7*	<.0001
ICU days	26.9 ± 37.3*	5.1 ± 10.3*	<.0001
LOS	67.3 ± 70.0*	19.9 ± 22.6*	<.0001
Surgeries	7.2 ± 6.5*	2.0 ± 3.1*	<.0001
MEU (mg/d)	145.5 ± 110.5*	80.7 ± 105.0*	<.0001
Pain score	3.0 ± 1.3	3.2 ± 1.6	.370

Soldiers receiving gabapentin or pregabalin had higher TBSA burned, injury severity scores (ISS), more days spent in the intensive care unit (ICU), and had longer length of hospital stay (LOS) compared with patients who did not receive an anticonvulsant. Those patients receiving gabapentin or pregabalin also received more morphine equivalent units (MEU) per day and underwent more surgeries than those who did not. There was no difference between the two groups in patient ages or pain scores.
* $P < .0001$.

Table 2. The relationship between gabapentin and pregabalin and PTSD

	Gabapentin or Pregabalin (n = 104)	No Gabapentin or Pregabalin (n = 186)	*P*
PCL-M score	33.3 ± 15.4	34.5 ± 15.7	.512
PTSD prevalence	26/104 (25.0%)	50/186 (26.9%)	.727

There is no difference between PTSD Checklist-Military (PCL-M) scores or PTSD incidence in patients who received gabapentin or pregabalin vs those who did not.

Table 3. Correlations between gabapentin or pregabalin receipt and patient demographics

	Gabapentin or Pregabalin (Yes/No)	
	rho	***P***
Age	0.072	.223
TBSA	0.430*	<.001
ISS	0.429*	<.001
ICU days	0.441*	<.001
LOS	0.493*	<.001
Surgeries	0.509*	<.001
MEU (mg/d)	0.412*	<.001
Pain score	–0.039	.513

Gabapentin or pregabalin receipt positively correlates with TBSA burned, injury severity scores (ISS), days spent in the intensive care unit (ICU), length of hospital stay (LOS), number of surgeries, and morphine equivalent units (MEU)/day. There was no difference between the two groups in patient ages or average pain scores.
* $P < .001$.

Table 4. Propensity score-matched patient demographics, injury severity parameters, and drugs received

	Gabapentin or Pregabalin (n = 57)	No Gabapentin or Pregabalin (n = 57)	*P*
Age	26.6 ± 6.1	25.3 ± 5.7	.133
TBSA	22.7 ± 18.5	22.7 ± 18.0	.885
ISS	16.6 ± 11.8	16.4 ± 12.0	.875
ICU days	15.7 ± 22.1	10.2 ± 14.3	.293
LOS	44.5 ± 40.4*	29.8 ± 29.9*	.041
Surgeries	5.5 ± 5.8†	2.9 ± 3.1†	.004
MEU (mg/d)	147.6 ± 116.6†	104.8 ± 169.2†	<.0001
Pain score	3.4 ± 1.5	3.0 ± 1.6	.278

After propensity score matching based on TBSA burned and injury severity score (ISS), subjects receiving gabapentin or pregabalin received significantly more morphine equivalent units (MEU) per day, had significantly longer hospital stays (LOS), and significantly more surgeries than the patients who did not receive gabapentin or pregabalin. Both groups had similar TBSA burned, injury severity scores (ISS), days spent in the intensive care unit (ICU), patient ages, or pain scores.
* $P < .05$.
† $P < .01$.

On the basis of these data, we performed propensity score matching on our patient sample based on two of the injury severity parameters, TBSA burned and ISS. The matched samples had no significant differences in age, TBSA, ISS, ICU days, or pain scores. However, subjects who received gabapentin or pregabalin still received significantly more MEU/day, underwent significantly more surgeries, and were in the hospital significantly longer than those who did not receive an anticonvulsant (Table 4). Again, there was no significant difference in the prevalence of a positive screen for PTSD between the two groups, $P = .663$. Thirteen out of the 57 (22.8%) patients who received gabapentin or pregabalin scored ≥44 on the PCL-M compared with 15 of 57 (26.3%) patients who did not receive an anticonvulsant (Table 5). There was also no significant difference in the average PCL-M scores of patients who received gabapentin or pregabalin and those who did not, $P = .887$ (Table 5).

DISCUSSION

PTSD is a significant health problem affecting a number of Servicemembers returning from the battlefield.[1] The nature of war places the Servicemembers in dangerous, life-threatening situations on a frequent basis and exposes them to near-constant stress, which puts them at risk for PTSD development.[5] Wounded warriors face additional challenges related to their injuries, including the potential for multiple surgeries and other medical procedures, exposure to a variety of drugs, uncontrolled pain, and lengthy rehabilitation. This is particularly true for patients who have suffered from severe burns, which require numerous debridements, excisions, grafts, and other painful, anxiety-generating procedures. Indeed, even in civilian burn centers, the incidence of PTSD after injury is significant, ranging from 8 to 45% of the burn patient population.[46–49]

Pharmacologic strategies to prevent or treat PTSD are not generally used in the burn center, and the primary indication for which gabapentin and pregabalin were prescribed was for pain. Pain management in a burn unit is complex and challenging. Patients receive a variety of medications to treat pain, including opioids, ketamine, nonsteroidal anti-inflammatory drugs, and acetaminophen. The biochemical mechanisms of these drugs, and numerous studies,

Table 5. Propensity score-matched analysis of the relationship between gabapentin or pregabalin and PTSD

	Gabapentin or Pregabalin (n = 57)	No Gabapentin or Pregabalin (n = 57)	*P*
PCL-M score	33.2 ± 15.4	33.7 ± 15.5	.887
PTSD prevalence	13/57 (22.8%)	15/57(26.3%)	.663

After propensity score matching based on TBSA burned and injury severity score (ISS), there is no difference between PTSD Checklist-Military (PCL-M) scores or PTSD incidence in subjects who received gabapentin or pregabalin vs those who did not.

suggest that they may possibly have effects on psychological disorders, including PTSD. In particular, opioids, ketamine, and anticonvulsants have been evaluated for their effects on psychological disorders, including PTSD.[13,16,19,28,41,45,50–52]

The development of PTSD in Servicemembers wounded in the combat environment is a serious problem for the Soldier and can significantly diminish the patients' quality of life and interfere with their social, family, and professional functions. PTSD in returning Servicemembers is also detrimental to the military because it can affect force readiness and return-to-duty rates. Thus, it is important to investigate potential pharmacologic and nonpharmacologic interventions that may reduce the rate of PTSD development or treat the symptoms of those patients diagnosed with the disease.

The search for an effective, reliable, and consistent pharmacologic agent for the prevention or treatment of PTSD is ongoing. Several families of drugs have been put forth as potential alternatives for these purposes, but few, if any, well-controlled and well-designed studies have supported altering the guidelines for pharmacologic treatments for PTSD. One class of drugs that has garnered much interest is anticonvulsants; it has been suggested that anticonvulsants could be used either as prophylactic agents to prevent PTSD development or as alternative treatments for PTSD.[16,28,53,54] We wanted to determine the relationship between the most commonly prescribed anticonvulsants, gabapentin and pregabalin, and the development of PTSD in burned Servicemembers.

Multiple retrospective studies have identified correlations between individual drugs and the subsequent development of PTSD. For example, one recent study revealed that receipt of perioperative ketamine was associated with significantly decreased prevalence of PTSD in burned Servicemembers (27 vs 46%).[45] However, there was no significant difference in prevalence of PTSD based on receipt of intraoperative ketamine identified in the subjects included in this study. In addition, a study of marines showed that those subjects who received the most morphine within 24 hours after injury had a decreased incidence of PTSD in comparison to those marines who did not receive morphine. This suggests that morphine reduces PTSD incidence but does not address the possibility that the decreased PTSD development may be related to effective pain control, or to effects on memory, rather than to an intrinsic property of the drug.[50]

Our data analyses suggest that there is no relationship between the anticonvulsants gabapentin and pregabalin and PTSD development. Despite the fact that subjects who received gabapentin or pregabalin suffered more severe injuries, as evidenced by significantly higher ISS, TBSA burned, days in the ICU, and LOS, they exhibited the same prevalence of PTSD as those subjects who did not receive gabapentin. Post hoc power analysis revealed that the power necessary to identify a difference in the groups was 0.088. Not surprisingly, as we did not detect a difference between the two groups, our power failed to reach this level. The computed power of this study was 0.055. However, the number of combat-burned Servicemembers requiring inpatient treatment at a burn center is relatively small, and we were unable to add additional subjects to the analysis.

For inclusion in the study, the Soldier must have completed a PCL-M at least 30 days after injury. This criterion biases the sample to a more severely injured population, because this population is more likely to be available for screening. The more severely injured Servicemembers may still be in the hospital or returning for treatments for 30 days or more postinjury. In addition, the patients who received gabapentin or pregabalin were significantly sicker than those who did not, raising concern that the analysis of PTSD incidence and symptom frequency and severity could be confounded by measures of injury severity. Thus, propensity score matching was performed based on ISS and TBSA burned. After matching, the two groups had similar ISS, TBSA, and ICU days. However, the group that received gabapentin or pregabalin still underwent significantly more surgeries, spent significantly more time in the hospital, and received significantly more opioids per day. The matched groups also exhibited similar incidence of PTSD and had similar average PCL-M scores and mean pain scores. We were unable to match based on all factors describing injury severity, and intuitively, it would seem that the sicker the patient, the more at risk they are for developing PTSD. However, the only consistently predictive risk factor for PTSD in military members is combat exposure.[55] In our patient population, this risk factor is shared by virtually all patients. Most of the patients in this study were evacuated from theater after blast exposure, often from improvised explosive devices or rocket-propelled grenades, to the burn center to undergo treatment.

This result is consistent with a double-blind, randomized controlled trial that found that neither gabapentin nor the beta-blocker propanolol affected subsequent PTSD development compared with placebo.[18] In an animal study, pregabalin was found to have acute anxiolytic effects but no effect on long-term development of PTSD-like symptoms.[52] Taken

together, these results suggest that gabapentin and pregabalin may not be effective at preventing PTSD development. Interestingly, Servicemembers who received gabapentin or pregabalin also received significantly more opioids per day. However, opioid dosage was not correlated to PTSD development or PCL-M scores. This is in contrast to the data suggesting that morphine administration was negatively correlated with PTSD development.[50] These contrasting data could be due to differences in timing of opioid administration. The Marine study focused on morphine administration during resuscitation and early trauma care, in level 1 and level 2 medical treatment facilities, whereas our data are taken from care given later in the treatment process at a level 5 definitive care facility.

Although a score of ≥44 on the PCL-M is a positive screen for PTSD, it is not a definitive diagnosis. A diagnosis of PTSD is usually based on results from screening tools together with evaluation of the DSM-IV criteria. However, because of the nature our patient population, we do not have access to patient psychiatric records or to their records once they exit our facility. It is likely that many of the high-scoring patients received psychological/psychiatric evaluation resulting in a true diagnosis of PTSD based on the DSM-IV criteria. However, we are unable to verify this. Patients scoring ≥44 were referred for additional care by the person administering and collecting the PCL-M.

Finally, the length of time between initiation of gabapentin or pregabalin treatment and PCL-M administration varied widely, as did the frequency and dosage of gabapentin and pregabalin. Although these factors could affect the efficacy of the drugs to treat/prevent PTSD, there are no data in the literature that suggest a dose/treatment length for PTSD. Because we do not have access to patient records before arrival or after discharge from the burn unit, we are unable to evaluate these questions with this population at this time. However, future studies investigating the efficacy of anticonvulsants for the treatment/prevention of PTSD are needed to determine whether there is an effective dosage range, frequency, and treatment length for this purpose.

CONCLUSIONS

We found no difference in PTSD prevalence in Servicemembers who received gabapentin or pregabalin vs those who did not. In addition, there was no significant difference in average PCL-M score between the two groups, indicating that each group experienced PTSD symptoms with similar severity and frequency. Despite suffering more severe burns, resulting in significantly higher TBSA burned, ISS, LOS, ICU days, number or surgeries, and opioid dosage, the group that received gabapentin or pregabalin did not screen positive for PTSD at a different rate than those patients who did not.

These data suggest that gabapentin or pregabalin administration may not affect PTSD development in burned Servicemembers. However, this study is a retrospective review and the amount and timing of gabapentin or pregabalin each patient received was not included in the data analysis. Each patient also received multiple other drugs and treatments during their hospital stays that may have affected their outcomes. The identification of consistently effective drugs for prevention and treatment of PTSD has yet to be accomplished.

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